General

Guideline Title

Chronic lymphocytic leukemia.

Bibliographic Source(s)

Alberta Provincial Hematology Tumour Team. Chronic lymphocytic leukemia. Edmonton (AB): CancerControl Alberta; 2013 Mar. 23 p. (Clinical practice guideline; no. LYHE-007). [61 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Hematology Tumour Team. Chronic lymphocytic leukemia. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2010 May. 21 p. (Clinical practice guideline; no. LYHE-007). [54 references]

Recommendations

Major Recommendations

Diagnosis and Prognosis

1. The initial diagnosis of chronic lymphocytic leukemia (CLL) relies on the detection of a circulating B-lymphocyte count *greater than or equal to* 5 x 10^9/L in the peripheral blood, for the duration of at least 3 months associated with a characteristic flow cytometry immunophenotype profile including CD19/CD5/CD23/CD43 positivity and cyclin D1 negativity. Small lymphocytic lymphoma is diagnosed when a lymph node or other tissue biopsy demonstrates a malignant lymphocytic infiltration with cells showing the same immunophenotype as CLL, but associated with a circulating B-lymphocyte count that *does not exceed* 5 x 10^9/L.
2. Flow cytometry for 70 kD zeta associated protein (ZAP-70) and CD38 expression should be performed at diagnosis to help with prognosis, and guide the frequency of follow-up visits and predict time to initial therapy.
3. Fluorescence in situ hybridization (FISH) cytogenetic analysis for del(17p) or del(11q) should be performed at the time when patients are started on first-line treatment. FISH analysis for del(17p) should be repeated at the time of second- or third-line therapy if patients are potential candidates for allogeneic stem cell transplantation or alemtuzumab.

First-Line Treatment Options

4. The majority of patients with early-stage CLL are managed initially with watchful waiting. The decision to initiate treatment should be based upon symptoms, advanced disease (bulky adenopathy/splenomegaly or cytopenias), or evidence for rapid disease progression (e.g., lymphocyte count doubling within 6 months).

5. Patient fitness and co-morbidities should be considered to determine whether aggressive treatments can be tolerated. In physically fit CLL patients who are able to tolerate more aggressive treatment, the combination of fludarabine + cyclophosphamide + rituximab (FCR) is recommended. The potential for toxicity of this regimen suggests that patients who have some co-morbidities may benefit from less aggressive treatments such as rituximab + fludarabine (FR) or chlorambucil + rituximab (CLB-R).
6. In frail patients with significant co-morbidities and competing causes of death, less toxic treatment options are warranted. In such cases, or if a patient declines intravenous treatment, oral chlorambucil is recommended as first choice, followed by oral fludarabine monotherapy as an alternative treatment.
7. Patients whose CLL possesses del(17p) usually do not respond to standard chemotherapy options for CLL. In such cases, alemtuzumab or early use of allogeneic stem cell transplantation could be considered as reasonable options.

Second-Line Treatment Options

8. In fit patients, FCR is an effective regimen for rituximab-naïve patients or fludarabine + cyclophosphamide (FC). Re-treatment with FCR is a reasonable treatment option for patients experiencing a long remission (more than 2 years) after initial FCR treatment.
9. The combination of fludarabine and low-dose alemtuzumab (FluCam) is a safe and effective therapy for relapsed/refractory CLL and has been demonstrated to improve progression-free survival (PFS) and overall survival (OS) compared to monotherapy with fludarabine.
10. In frail patients, fludarabine or chlorambucil are reasonable second-line treatment options. If the initial remission is greater than 1 year, re-treatment with the initial chemotherapy agent is recommended. If the initial remission is shorter than 1 year, treatment with a different second-line agent is indicated.
11. Allogeneic stem cell transplantation may also be considered for fit patients who are younger than 65 years of age and who have not responded to therapy, have progressive disease within 1 year of fludarabine treatment or within 2 years of fludarabine-based combination treatment, or those whose CLL possesses del(17p) and require treatment.
12. Chemo-sensitivity should be demonstrated prior to stem cell transplantation. Several small studies have reported encouraging response rates after treatment with high-dose corticosteroids in patients with refractory CLL or in patients with del(17p).

Follow-up and Supportive Care

13. Patients with CLL often have compromised immune systems due to either the disease itself and/or the associated treatments. Antibiotic prophylaxis and regular vaccinations are recommended, depending on the type of treatments administered. *Pneumocystis jiroveci* pneumonia (PCP) and anti-viral prophylaxis are strongly recommended for all patients receiving FCR or FluCam. Patients treated with alemtuzumab should also be screened for cytomegalovirus (CMV) reactivation with weekly CMV polymerase chain reaction (PCR) assay.
14. Special attention should be paid to the appearance of autoimmune cytopenias, such as autoimmune hemolytic anemia, immune thrombocytopenia purpura, and pure red-cell aplasia, which occur in up to 11 percent of patients with CLL.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Chronic lymphocytic leukemia

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Hematology

Oncology

Radiation Oncology

Intended Users

Physicians

Guideline Objective(s)

To evaluate the diagnostic and staging criteria, treatment strategies, and follow-up and supportive care practices for adult patients in Alberta with chronic lymphocytic leukemia

Target Population

Adults over 18 years of age with suspected or confirmed chronic lymphocytic leukemia

Note: Different principles apply to pediatric patients.

Interventions and Practices Considered

Diagnosis/Evaluation

1. Detection of a circulating B-lymphocyte count greater than or equal to 5 x 10^9/L in the peripheral blood
2. Flow cytometry immunophenotype profile including CD19/CD5/CD23/CD43 positivity and cyclin D1 negativity
3. Flow cytometry for 70 kD zeta associated protein (ZAP-70) and CD38 expressions
4. Fluorescence in situ hybridization (FISH) cytogenetic analysis for del(17p) or del(11q)

Treatment/Management

1. First-line treatment options
    - Watchful waiting
    - Combination of fludarabine + cyclophosphamide + rituximab (FCR) or rituximab + fludarabine (FR) or chlorambucil + rituximab (CLB-R)
    - Oral chlorambucil followed by oral fludarabine monotherapy as an alternative
    - Alemtuzumab or early use of allogeneic stem cell transplantation
2. Second-line treatment options
    - FCR for patients naïve to rituximab or fludarabine + cyclophosphamide (FC)
    - Re-treatment with FCR
    - Fludarabine + low-dose alemtuzumab (FluCam)
    - Fludarabine or chlorambucil
    - Re-treatment with the initial chemotherapy agent or treatment with a different second-line agent
    - Allogeneic stem cell transplantation
3. Follow-up and supportive care
    - Antibiotic prophylaxis and regular vaccinations
    - *Pneumocystis jiroveci* pneumonia (PCP) and anti-viral prophylaxis for all patients receiving FCR or FluCam
    - Screening for cytomegalovirus (CMV) reactivation in patients treated with alemtuzumab
    - Special attention to the appearance of autoimmune cytopenias

Major Outcomes Considered

- Accuracy of diagnosis and staging
- Response rate
- Survival rates (overall, progression-free, 5-year)
- Morbidity

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

- What are the recommended diagnostic and staging criteria for adult patients in Alberta with chronic lymphocytic leukemia (CLL)?
- What are the recommended treatment strategies for adult patients in Alberta with newly diagnosed, relapsed, or refractory CLL?
- What are the recommended follow-up and supportive care practices for adult patients in Alberta with CLL?

Search Strategy

An updated review of the literature was conducted by searching journal articles using the Medline (1950 to March Week 1, 2013), EMBASE (1980 to March Week 1, 2013), Cochrane Database of Systematic Reviews (1st Quarter, 2013), and PubMed electronic databases. The MeSH heading "Leukemia, Lymphocytic, Chronic, B-Cell" was combined with the search terms "drug therapy" and "therapy". The results were limited to adults, practice guidelines, systematic reviews, meta-analyses, multicentre studies, randomized controlled trials, and clinical trials. Articles were excluded from the final review if they: had a non-English abstract, were not available through the library system, or were published before the year 2000. The references and bibliographies of articles identified through these searches were scanned for additional sources. A search for practice guidelines published since January 2000 was conducted by accessing the Web sites of the following organizations: Cancer Care Ontario, British Columbia Cancer Agency, the National Comprehensive Cancer Network, the European Society for Medical Oncology, and the Italian Society of Hematology/Italian Group for Bone Marrow Transplantation.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulate the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Portions of this guideline document were adapted, with permission, from recommendations developed by a steering committee consisting of hematologists from across Canada.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it will be sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Portions of this guideline document were adapted, with permission, from recommendations developed by a steering committee consisting of hematologists from across Canada.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of chronic lymphocytic leukemia

Potential Harms

- Toxicity and side effects of therapy, including hematological toxicity, neutropenia, leukocytopenia, cytomegalovirus events, and infusion-related reactions
- Patients with chronic lymphocytic leukemia often have compromised immune systems due to the disease itself and/or its associated treatments. Infections are therefore common, and prophylaxis is appropriate, depending on the type of treatment given.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Discuss the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2010 May (revised 2013 Mar)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

There was no direct industry involvement in the development or dissemination of this guideline.

Guideline Committee

Alberta Provincial Hematology Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Hematology Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, hematologists, nurses, pathologists, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Hematology Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Hematology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on April 28, 2014. The information was verified by the guideline developer on June 6, 2014.

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